Research Proposal of the Thesis Entitled

Cost Benefit Analysis of Genome Sequencing For Healthcare Providers In India

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by

Submitted

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1. Introduction

Genome sequencing is a genetic technique that helps us read the DNA of an organism. Timely advancements in its technology have led us to use genome sequencing as a "tool" in diagnosis and healthcare facilities. Therefore, genome sequencing has recently transformed healthcare, providing unparalleled knowledge about human biology, disease vulnerability, and tailored treatment.

Genome sequencing has proven to be an invaluable tool in diagnosing genetic diseases, predicting disease risks, and formulating care choices. Nevertheless, genome sequencing services remain in the early stages in India, and most medical laboratories do not provide them.

A pilot study was conducted to find out why many laboratories in India do not offer genome sequencing services.

Thirty-three NABL-certified laboratories were contacted telephonically across the country to determine the most significant barriers to entry into the genome sequencing industry. Most respondents (82%) indicated that concerns about revenue generation and substantial initial investment are the two most important factors preventing them from doing so.

Based on the pilot study data, we designed the present study to investigate the cost-benefit analysis associated with healthcare providers and laboratories in India. The study will compare the expected costs and projected benefits of developing genome sequencing facilities and determine whether benefits exceed costs.

Along with the cost-benefit analysis (CBA), the break-even point (BEP), payback period (PBP), return on investment (ROI), net present value (NPV), and profitability index (PI) will be measured to check the efficiency and long-term sustainability of the genome sequencing business.

The findings of this research have the potential to inspire healthcare providers to make an informed decision on adopting genome sequencing as a standard diagnostic tool in India. This could lead to significant improvements in overall healthcare and medical facilities, including the development of futuristic personalized medicine. The research outcomes can help make genome sequencing mainstream in India.

In addition, overall diagnosis can be improved, treatments can become more effective, and the quality of the entire healthcare system in India can be enhanced. Moreover, adopting genome sequencing will be beneficial in generating new jobs, thereby improving the overall economy. Educational facilities can also be improved as they have to incorporate genome sequencing and related topics in their curriculum. In conclusion, the adaptation of genome sequencing will not only help improve healthcare but also the education system, research, and overall economy of India.

2. Pilot Study

A pre-research pilot study investigated the key problems medical laboratories face in offering genome sequencing services in India.

The idea was to find out the main roadblock. A few NABL-accredited laboratories (33) have been selected for the pilot study. Selection criteria were geographical location, size, and service portfolio offered by the laboratories. These laboratories were certified by the National Accreditation Board for Testing and Calibration Laboratories (NABL) to adhere to stringent quality standards. Hence, the quality standard among the sample group is uniform- the highest quality with best practices.

The pilot study was structured around two distinct groups: laboratories that offer the genome sequencing service (group 1) and those that do not (group 2). Group 1 participants were interviewed about the challenges they face in implementing genome sequencing services, while Group 2 participants were asked about their reasons for not offering these services. The interview medium for the pilot study was telephone communication.

The study's results are listed here:

- In India, 27 out of 33 (82%) participants demonstrated uncertainties associated with revenue generation and the requirement of substantial initial investment. We identified the present outcome as a primary challenge.
- 4 out of 33 (12%) narrated about not having an adequate customer base.
- 1 out of 33 (3%) was concerned regarding the lack of trained professionals (bioinformaticians, geneticists and lab personnel).

- Another 1 out of 33 (3%) participants highlighted the doctor's limited knowledge of genome sequencing and low interest in recommending such tests.

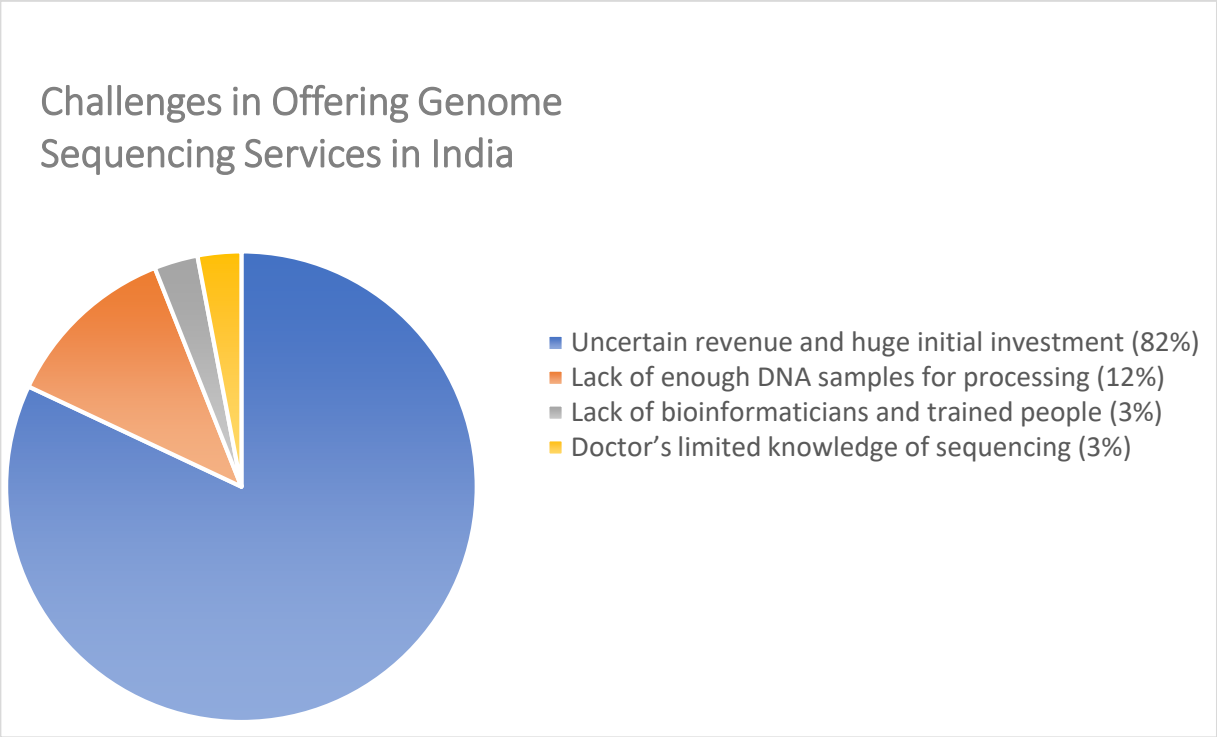
Challenges in Offering Genome Sequencing Services in India
Uncertain revenue and huge initial investment (82%)
Lack of enough DNA samples for processing (12%)
Lack of bioinformaticians and trained people (3%)
Doctor's limited knowledge of sequencing (3%)

Figure 1: Challenges in Offering Genome Sequencing Services in India

The study uncovered several important findings, as follows:

- An overwhelming majority of respondents (82%) identified uncertainties associated with revenue generation and substantial initial investment requirements as significant challenges to providing genome sequencing services in India.
- Revenue generation uncertainties act as a primary obstacle, deterring organizations from investing in genome sequencing services without a clear understanding of potential revenue streams and a sustainable business model.
- Furthermore, the huge initial investment required limits the capability of laboratories to offer genome sequencing services.
- Despite genome sequencing's transformative potential in healthcare, establishing and maintaining the necessary infrastructure and expertise requires significant financial resources.

- The substantial initial investment for equipment, laboratory setup, and trained personnel poses a significant barrier for medical laboratories in India.
- Many insurance companies do not cover the cost of genome sequencing, making it difficult for patients to access these services. The absence of a clear reimbursement policy discourages laboratories from investing in genome sequencing technology and services.

The pilot study served as a valuable foundation for the main research project, illuminating the areas that require further exploration. It highlighted the importance of conducting a thorough analysis of the costs and benefits associated with the adoption of genome sequencing technologies in India.

3. Literature Review

A detailed literature review was conducted to understand the research work done for implementing genome sequencing technology into routine health care across the world.

Here's the overview of the literature review process.

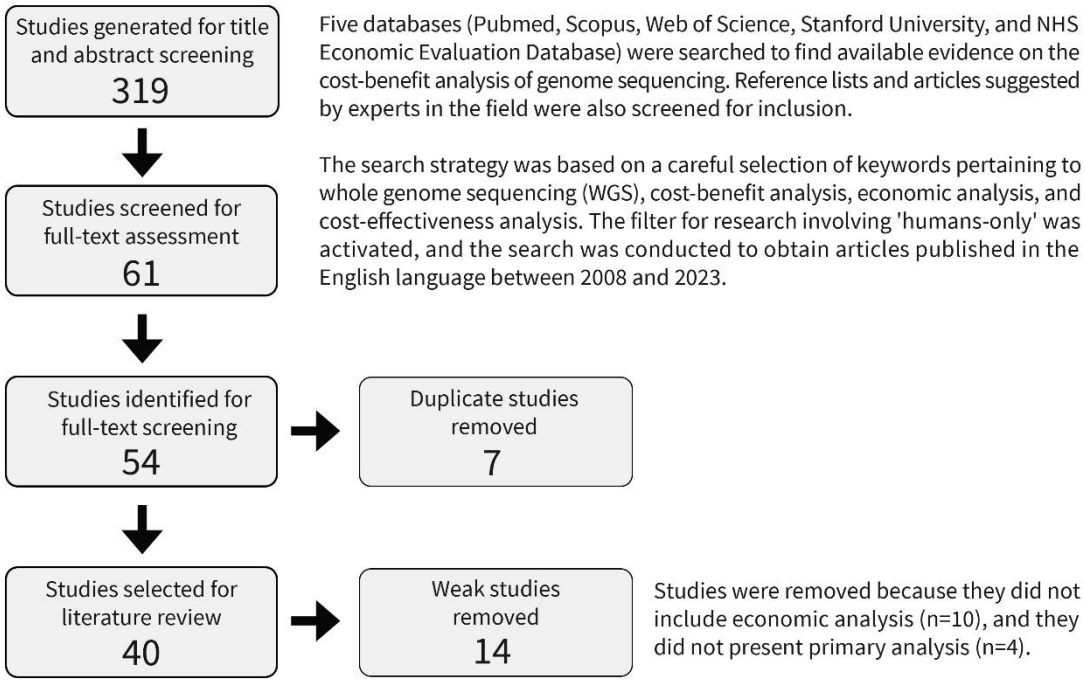
Studies generated for title and abstract screening
319
Five databases (Pubmed, Scopus, Web of Science, Stanford University, and NHS Economic Evaluation Database) were searched to find available evidence on the cost-benefit analysis of genome sequencing. Reference lists and articles suggested by experts in the field were also screened for inclusion.
Studies screened for full-text assessment
61
The search strategy was based on a careful selection of keywords pertaining to whole genome sequencing (WGS), cost-benefit analysis, economic analysis, and cost-effectiveness analysis. The filter for research involving 'humans-only' was activated, and the search was conducted to obtain articles published in the English language between 2008 and 2023.
Studies identified for full-text screening
54
Duplicate studies removed
7
Studies selected for literature review
40
Weak studies removed
14
Studies were removed because they did not include economic analysis (n=10), and they did not present primary analysis (n=4).

Figure 2: Literature Review Process

* Author's creation

A brief record of the same has been narrated below.

Genome sequencing is the process of reading and determining the nucleotides A, T, C, and G (Adenine, Thaimin, Cytosine, and Guanin) within an organism's DNA. It has emerged as a cornerstone of modern genetic research and clinical practice. Genome sequencing became accessible, affordable and high-throughput only after the completion of the Human Genome Project in 2003. HGP was the paramount milestone in the genome sequencing industry that revolutionized the field of genetics. Now we can study genetic variants, and disease mechanisms and personalize medical possibilities (Lander et al., 2001; Schuster, 2008). The genetic information pre-existed in the patient's sample can now be accurately decoded and read. Clinicians from the medical diagnostics industry can now study rare to complex genetic disease conditions like cancer and heart disease and, identify and determine disease-causing genes and mutations, predict disease risk, and prepare a personalized treatment plan according to the data. Thereby, it improves the overall diagnostic accuracy, prognosis assessment and treatment decision (Collins et al., 2003; Ashley, 2015).

Medical laboratories equipped with high-throughput and cutting-edge sequencing platforms, state-of-the-art and extensive bioinformatics setup (computational requirement and manpower) and skilled personnel play a significant role in bridging between the power of sequencing information and clinical practices. By performing the genome sequencing assays, analyzing the sequencing data, concluding the finding and delivering the finding to clinicians, hospitals, medical centers or even research centers, they fulfill the diagnostic and patient care needs (Schuster, 2008; Manolio et al., 2009).

Due to such efforts, genome sequencing can be integrated into standard clinical practices. However, medical laboratories encounter both opportunities and challenges, at the same time, to use genome sequencing effectively. Using the full potential of genome sequencing for precise diagnosis, targeted therapy, and disease prevention requires not only technical expertise and infrastructure but also robust quality control schemes, ethical considerations, and constancy with regulatory standards. Therefore, understanding genome sequencing technologies, their applications in medical diagnostics, and the role of medical laboratories is

essential for advancing healthcare delivery and realizing the promise of personalized medicine (Ashley, 2015; Manolio et al., 2009).

The present review majorly focuses on these points and discusses the evolution, applications, economic implications, challenges, opportunities and strategies to implement genome sequencing into routine clinical care.

Genome sequencing technologies made a remarkable appearance during the initiation of the Human Genome Project (HGP) in early 1990. The first draft of the human genome sequence was published in 2001, publically. However, the labor-intensive and costly nature of Sanger sequencing limited the scale and scope of genome sequencing efforts. The approximate stated cost of human genome sequencing in 2001 was around $100 Million and was drastically reduced to $1000 till now (Lander et al., 2001; National Human Genome Institute, 2022). The completion of the Human Genome Project (HGP) established the foundation for a new era in genome sequencing marked by rapid technological innovation and exponential growth in sequencing.

The introduction of next-generation sequencing (NGS) technologies in the mid-2000s completely revolutionized genome sequencing methodologies. Platforms like Illumina's HiSeq and MiSeq, Roche's 454 sequencing, and Life Technologies' Ion Torrent brought about massively parallel sequencing capabilities, enabling the simultaneous sequencing of millions of DNA fragments in a single run (Metzker, 2010; Stratton M, 2009). Year by year, genome sequencing technology not only becomes cheaper but also faster and high throughput. The following figure shows the improvement in the throughput after each year. Before 2000, scientists could hardly sequence 10,000 nucleotides a day, with manual sample preparation and sequencing. However, with recent advancements and automation in sample preparation, now scientists can generate more than 10 million nucleotides raw day in a day (Stratton M, 2009).

Researchers at Stanford Medicine achieved the Guinness World Record title for the fastest DNA sequencing technique in the world. They sequenced a human genome in just 5 hours and 2 minutes. Usually, it takes around 26 hours to get results with the recent technologies. Whereas, in the 1990s, scientists took 13 years, from 1990 to 2003, to successfully sequence a complete human genome (Stanford Medicine, 2022). The advancement in faster, cheaper and high-throughput next-generation sequencing revolutionized genetics and genomics studies and by penetrating into the clinical and healthcare setup (Hayeems and Dimmock et al., 2020).

Large-scale and genome-wide studies are now possible as the NGS drastically reduced the sequencing TAT (turn-around time) and cost. Pacific Biosciences's and Oxford Nanopore Technologies' single-molecule and real-time sequencing technology (SMRT) offer long-read sequencing with ultra-high throughput. The emergence of third-generation sequencing platforms like SMRT technologies benefits minimal sample preparation and real-time data generation (Goodwin et al., 2016).

The combined applications of SMTR and long-read sequencing transformed genome sequencing by providing better genome assembling, structural variant detection and epigenetic analysis. Furthermore, third-generation sequencing also enabled comprehensive single-cell profiling by single-cell RNA sequencing (scRNA-seq), single-cell DNA sequencing (scDNA-seq) and transcriptomics, and unlocked cells and tissue-specific gene expression studies (Tang et al., 2009; Stoeckius et al., 2017). In conclusion, from labor-intensive first-generation sequencing to high-throughput second-generation sequencing the throughput, speed and accuracy of sequencing increased substantially. Whereare, the advances in third-generation SMTR and long-read sequencing also allowed us to understand the genome complexity at a single-cell level.

Genome sequencing has a wide variety of applications starting from plant research to pathogen studies, and animal research to human diagnosis. However, before 2020, the genomic and genetic applications of genome sequencing were limited. Yet again, because of the substantial cost, speed and TAT. After, it has been offered into the clinical and healthcare fields (Green & Guyer, 2011). In particular, it has been used for disease diagnosis, prognosis and treatment interventions in clinical setups. One major and preliminary application of genome sequencing in medical laboratories is diagnosing genetic disorders and rare diseases. By analyzing an individual's genome, laboratories can pinpoint disease-causing mutations, variants, and copy number variations associated with conditions like cystic fibrosis, muscular dystrophy, Huntington's disease (Biesecker & Green, 2014), etc.

In addition to the diagnosis of genetic disorders, genome sequencing facilitates pharmacogenomic testing, allowing clinicians to advise medication options as per an patient's genetic profile. Pharmacogenomic testing evaluates genetic variants affecting drug metabolism, efficacy, and toxicity, guiding drug selection, dosage adjustments, and adverse event management. Laboratories offer pharmacogenomic testing panels targeting genes

involved in drug metabolism pathways, optimizing pharmacotherapy and minimizing adverse reactions (Caudle et al., 2020).

The most extensive applications of genome sequencing are in cancer research and oncology, nowadays. Target gene sequencing, whole-genome tumor profiling, whole-exome sequencing, circulating tumor DNA sequencing and smaller non-coding RNA sequencing are a few popular techniques used for various cancer studies. It is employed for cancer research, diagnosis, prognosis, disease progression and treatment intervention (Roychowdhury et al., 2016). Germline and cell-free fetal DNA sequencing further allows prenatal screening and oncology and epigenetic investigations for various purposes (Christensen and Dukhovny et al., 2015). Moreover, the same sequencing technology also enables microbial studies, pathogen identification, infection, outbreak and antibiotic resistance investigations (Köser et al., 2012).

Genome sequencing setup cost, cost-saving and expected revenue are the major concert to establish such facilities in a medical laboratory. Initial setup costs for infrastructure development, instrumentation and manpower pose additional development challenges (Phillips et al., 2017). For medical laboratories, it overcomes the requirement of multiple tests for a single condition. A single genome sequencing test data provides comprehensive information regarding the condition and thus it not only streamlines the diagnostics but also reduces unnecessary testing expenditure (Manzoni et al., 2020; Phillips et al., 2017). The streamlined testing facility saves the cost for the laboratory.

One pivotal inclusion of genome sequencing in personalized medicine can also reduce significant costs by providing personalized and precision medicine options. In addition, the omission of the trial-and-error approach, improved testing efficiency and minimized adverse drug effects would collectively improve the testing penetrance, thereby providing more revenue options for genome sequencing laboratories (Caudle et al., 2020). Two important characteristics of the present technology— scalability and automation make genome sequencing increasingly available with a cost-effective approach for routine testing. Previous studies suggest that the genome sequencing cost is continuing to decrease with increasing throughput (Manzoni et al., 2020). Nonetheless, various scattered studies demonstrated that genome sequencing costs can only be reduced up to affordability only if the consumables and utilizes are available at a lower cost (Schwarze and Buchanan et al., 2019). Cost-effectiveness analysis by micro-costing method also demonstrated that the overall testing cost can further be reduced if micro-costing is implemented keenly. Note that micro-costing is a process of

primary data collection to measure the use of resources such as staff time using direct observation, staff activity logs, or survey methods (Grosse and Gudgeon, 2021).

Despite having extensive initial investment, establishing a genome sequencing facility from scratch either into a new or existing facility is indeed a challenging task. It majorly includes, technical, logistics, infrastructure, financial, regulatory and ethical challenges.

One prominent roadblocker faced by genome sequencing facility are technical challenges. Genome sequencing generates a huge amount of data, that needs, state-of-the-art and sophisticated bioinformatics setup and manpower. It includes data processing pipelines, softwares and programs, and computations infrastructure (Rehm et al., 2013). Furthermore, expert's knowledge and multidisciplinary collaboration between geneticists and clinicians is also mandatory to study and interpret the complex data generated during sequencing.

Logistic challenges includes, sample acquisition, collection and storage, accreditation and certification, robust workflow and protocol development and managing utilities and constumables timely (Hegde et al., 2017). Regulatory and ethical issues are also a least but important challenges in implementing the genome sequencing. Data, privacy, testing concern, data sharing policies, legal and judiciary issues should be addressed within the policies and regulations of the government (Green & Guyer, 2011). Moreover, the testing should follow internation and uniform standards, compliances and ethical boundries (Burke et al., 2015). Implementing genome sequencing within the confines of financial constraints and reimbursement policies is one of several practical barriers preventing it from becoming a standard option in even resource-limited healthcare settings. Wide variation in reimbursement policies and rates for genomic testing services contribute to the uncertainty around whether, who and how people can obtain genetic/genomic testing - with those most directly at concern being underserved suitable populations or rare diseases (Phillips et al., 2017).

Despite having challenges and investment drawbacks, the genome sequencing setup creates varied lucrative opportunities. A single sequencing test is capable enough to study many different conditions by only looking into a patient's DNA. Through this, the TAT can be reduced while the accuracy and diagnostic output can be increased, greatly (Manolio et al., 2019). It also allows therapeutic innovations, clinical trials, drug discoveries, biomarker studies and end-patient care by providing comprehensive data (Chakravarty et al., 2017). Conclusively, the population's overall public health and health outcomes can be improved by

identifying population-based genetic risk factors, predictive genomics and annotating common population-based pathogenic variants (Manrai et al., 2016).

However, literature and research scarcity on cost-effective, cost-benefit and returns of investment studies limits the penetrance of genome sequencing in mainstream healthcare. A comprehensive and extensive study on viability, cost-effectivity, sustainability, and affordability helps healthcare providers or medical laboratories to adapt or upgrade their existing facilities with genome sequencing technology. The present study has been designed to fill this gap by comprehensive (qualitative and quantitative) analysis of genome sequencing and cost-benefit analysis for medical laboratories in India.

4. Problem Definition

The list of NABL-accredited laboratories does not specify the exact number of laboratories in India that offer genome sequencing services. However, the AI-based search results indicate that out of the 2150 total labs in India in 2024, only 68 labs currently offer genome sequencing services. The main reasons that only a few laboratories offer genome sequencing services in India are primarily related to substantial initial investment requirements and uncertainties associated with revenue generation. Most healthcare providers are still not sure about the financial viability of the genome sequencing business.

5. Research Gap

Although the authors of the current literature have studied the scientific aspects of genome sequencing, research on its cost-benefit analysis still needs to be done. It is crucial to compare the projected costs and anticipated benefits of genome sequencing services to know whether the benefits exceed the costs or not. The field of genetics has not adequately explored this area of research, necessitating further investigation.

6. Research question

Q1.What are the direct and indirect costs associated with implementing genome sequencing technology for health providers in India?

Q2.How do the benefits of genome sequencing, outweigh the initial costs for healthcare providers in India?

Q3.What are the key challenges faced by healthcare providers in India in integrating genome sequencing into their clinical practices?

7. Need and Significance of the study

Most medical laboratories in India face the major challenges associated with substantial initial investment requirements and uncertain revenue generation to implement genome sequencing services in India. The result of this research can help hospitals, laboratories, and academic institutions decide whether it is financially beneficial to offer genome sequencing services or not.

8. Research Objectives

The present study is designed:

1. To identify the total cost involved to develop genome sequencing services to new labs and to existing labs in India.
2. To identify the key challenges which existing labs are facing to implement genome sequencing services.

3.To analyse the cost and benefits associated with genome sequencing in India.

9. Research Hypothesis

H01: Cost associated with Genome Sequencing have no impact on the implementation of these services to new labs in India.

Ha1: Cost associated with Genome Sequencing have an impact on the implementation of these services to new labs in India.

H02: Cost associated with Genome Sequencing have no impact on the implementation of these services to existing labs in India.

Ha2: Cost associated with Genome Sequencing have an impact on the implementation of these services to existing labs in India.

H03: Existing Labs in India are not facing challenges to implement genome sequencing.

Ha3: Existing Labs in India are facing challenges to implement genome sequencing.

H04: Benefits of genome sequencing implementation will not outweigh the initial costs for healthcare providers in India.

Ha4: Benefits of genome sequencing implementation will outweigh the initial costs for healthcare providers in India.

10. Research Methodology

The following figure exhibits the overview of research methodology process.

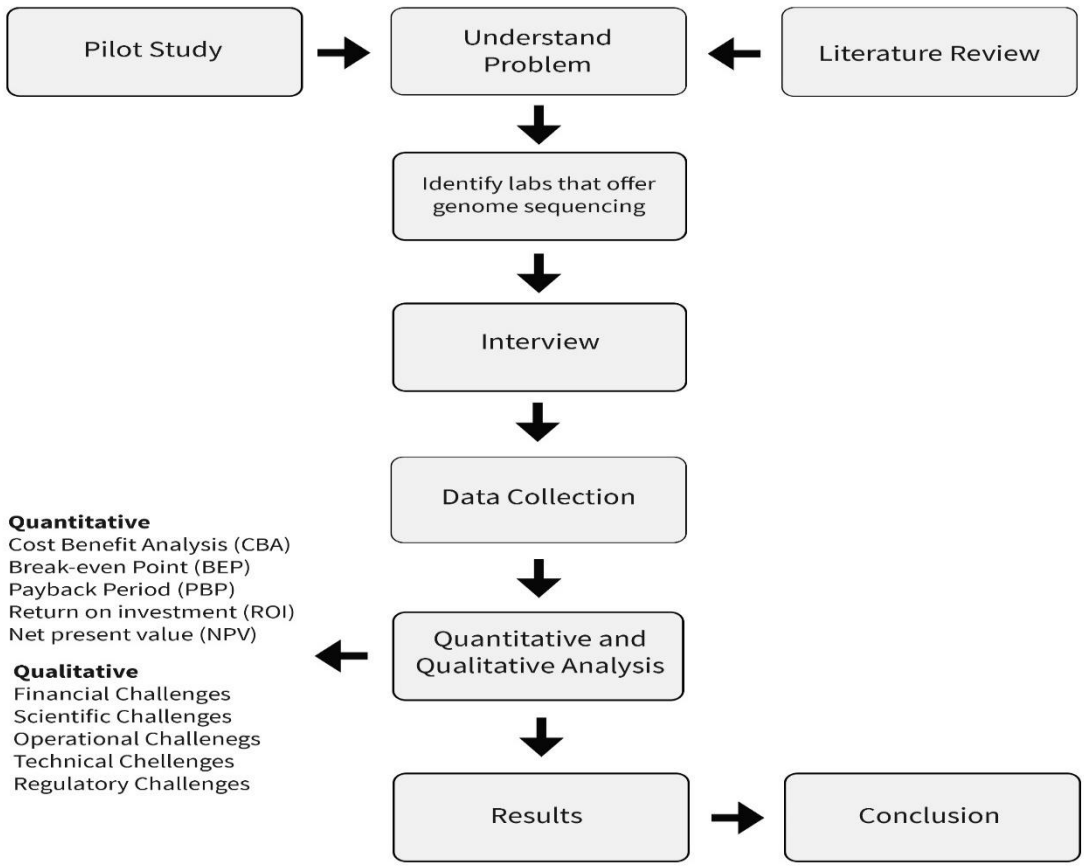

Figure 3: Research Methodology Process

* Author's Creation

The present research includes a qualitative and quantitative methodology for performing a cost-benefit analysis for genome sequencing services. A minimum of 35 out of 68 NABL-approved laboratories that offer genome sequencing services in India will be contacted and requested to

provide information. The data will be collected via personal interviews, financial reports, equipment manufacturer quotations, and equipment manufacturer websites.

The cost calculation will include the following:

Table 2: Types of Costs

Type of Cost	Particulars
Fixed Costs	NGS machine, Microscope, Restriction Enzymes, Pipettors, Freezers, Incubators, Shakers, Hot plates, Glassware, Plasticware, Computers, Software, Database, Government approvals, Furniture, Stationary
Variable Costs	Human resource, DNA test kit, Sample collection, Advertisement, Taxes, etc.
Indirect Costs	Rent, Electricity, Administrative Overheads
Intangible Costs	Decline in machine value due to technology advancement, decline in employee productivity, and other unexpected costs
Opportunity Costs	Interest cost, Lost opportunities that arise when a company chooses genome sequencing over other business pursuits.
Costs of Potential Risks	Regulatory risks, Competition, Scientific challenges, etc.

The benefit calculation will include direct benefits, indirect benefits, competitive benefits, and intangible benefits. After calculating the total cost and benefits of genome sequencing, the cost-benefit analysis will be performed. Along with the cost-benefit analysis, break-even Point (BEP), payback Period (PBP), return on investment (ROI), net present value (NPV), and profitability Index (PI) will be calculated.

11. Visible Research Outcomes

Genome sequencing can revolutionize healthcare in India by fostering personalized medicine, detecting disease in its early stage, and contributing valuable data for global research. The outcomes of this study will help healthcare providers make data-driven financial decisions, raise investment funds, and incorporate genome sequencing technology into mainstream clinical care practice. It will improve overall diagnostic accuracy, Turnaround (TAT) time, and treatment effectiveness, benefiting millions across India. It will also create new career opportunities in the biomedical field, offering a promising future for genetics professionals in this sector.

12. Tentative Chapter Plan

1. Introduction
2. Review of Literature
3. Research methodology
4. Data Analysis & Interpretation
5. Research Conclusions & Suggestions

13. Limitations of the Study

Determining the cost of genome sequencing services is a challenge due to the variability in cost structure. Factors such as the sequencing platform, manufacturer of equipment, number of DNA samples to be processed, and costs associated with data analysis contribute to this variability.

Furthermore, calculating the potential benefits of genome sequencing services is also challenging. This is because India's genome sequencing field is relatively new, resulting in a limited availability of data necessary for reliable projections of benefits.

The study also has limitations because of the small sample size. The limited number of medical laboratories are willing to divulge their financial details for research purposes.

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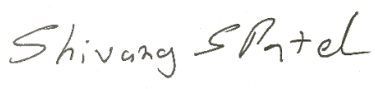

Signature of the Research Scholar

Signature of the Research Supervisor